REMARKS

Claims 33, 34, and 46-49 are pending in the application. Claims 33, 34, and 47 have been cancelled by this amendment. New claims 50-59 have been added to the application. Therefore, claims 46 and 48-59 are at issue.

New claims 50-59 find support in originally filed claims 33 and 34. Claim 50 is essentially claims 33 and 34 written in independent form, and the individual stress-inducing events of claim 34 are recited individually in claims 51-59. Claims 46 and 48 have been amended to correct the pendency of these claims.

The examiner has issued an obviousness-type double patenting rejection over applicants' issued parent application, i.e., U.S. Patent No. 6,593,353. In response, applicants again submit that a terminal disclaimer over U.S. Patent No. 6,593,353 ('353) is not proper because the present application is a divisional of the parent application. The USPTO, by issuing a restriction requirement in the parent case, already determined that the present invention is patentably distinct from the invention claimed in the parent application.

The examiner states it is not clear in the absence of the original restriction requirement that the present claims are distinct from the '353 patent claims. In response, applicants enclose the restriction requirement from the '353 file, and applicants' response, concurrently with this amendment. Note that the restriction requirement mandated the election of a single "specific disease condition." In response, applicants elected "a p53-deficient cancerous tumor."

The issued claims in the '353 patent are directed only to such cancer treatments. *All* other disease states recited in original claim 34 were withdrawn from consideration and are being prosecuted in the present application. The recited feature in claim 34 of "a cancer treatment" (and in the claims of the '353 patent) is *not* recited in new claim 50.

Because the USPTO previously decided that the claims of the '353 patent and the claims of the present application are directed to independent inventions, the USPTO now cannot retreat from that decision and issue an obviousness-type double patenting rejection. Applicants, therefore, submit that the obviousness-type double patenting rejection of claims 46 and 48-50 over coowned U.S. Patent No. 6,593,353 is improper and should be withdrawn.

Claims 33, 34, and 46-49 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. In view of the amendments to the claims, it is submitted that this rejection has been overcome. In particular, new claim 50 is recited as suggested by the examiner, and claims 33 and 34 have been cancelled.

Claims 33, 34, and 46-49 stand rejected as being anticipated under 35 U.S.C. §102(b) over Murase et al. U.S. Patent No. 4,497,817 ('817). The rejection is based on the contention that because the '817 patent discloses a compound that suppresses rejection of a tissue transplant, the compound would inherently prevent cell death or allow a cell to recover from a stress-inducing event of tissue transplant. It is submitted that this rejection is in error, and should be withdrawn.

In particular, the '817 patent is directed to compounds exhibiting an immunoregulatory action. In fact, the '817 patent is directed *solely* to immunoregulation and use of the disclosed compounds as an anti-allergic agent, an antiasthmatic, and a suppressant of tissue transplant rejection. The '817 patent is silent with respect to p53 inhibition, let alone reversible p53 inhibition. The use of a reversible p53 inhibitor to allow normal cells to recover *prior* to transplanting a tissue or organ (claim 50) or to *prepare* a host for a bone marrow transplant (claims 50 and 46) is totally unrelated to immunosuppression after a tissue is transplanted.

It is known that a person preparing for a bone marrow transplant often is treated with a chemotherapeutic agent. This a stress-inducing event can lead to the death of *normal cells* via p53 activation. By administering a temporary p53 inhibitor, p53 cannot be activated and the normal, but stressed, cells will not be killed. This mode of action is not related to immunosuppression, but is an entirely different pathway. See '817 patent, column 3, line 29 through column 4, line 10, which describes the mode of action of the '817 compounds.

An immunosuppressive agent as disclosed in the '817 patent is administered to reduce the occurrence of organ rejection by the host. The '817 compounds are administered *after* transplantation to suppress rejection. See '817 patent, column 4, lines 14-29, wherein administration of the compounds is disclosed. If administered in the manner disclosed in the

'817 patent, the benefits of the present invention would not be realized.

In the present claims, a reversible p53 inhibitor is administered in a tissue or organ transplanting situation to *protect* the tissue or organ prior to transplanting (see specification, page 6, lines 7-8). The present claims are not directed to reducing tissue rejection *after* transplanting, as described in the '817 patent. A reversible p53 inhibitor is administered in the present invention to protect normal cells from death attributed to a stress-inducing event. This is unrelated to a host rejecting a transplanted organ. In particular, an immunosuppressive agent could be administered with a reversible p53 inhibitor in order to reduce the occurrence of organ rejection *and* to protect normal cells from a stress-induced death.

Accordingly, as previously discussed with the examiner, the present invention is directed to the reversible inhibition of p53 to protect normal cells from death attributable to a stress-inducing event, as opposed to immunosuppression. Therefore, the '817 patent is not relevant to the present application.

In summary, the methods recited in the present claims are substantially different from the methods disclosed in the '817 patent, and, therefore, it is submitted that claims 46 and 50 are neither anticipated under 35 U.S.C. §102(b) nor obvious under 35 U.S.C. §103 over the '817 patent. The '817 patent is totally silent with respect to using a temporary p53 inhibitor to prevent normal cell death attributable to a stress-inducing event, either generally or from the events recited in claims 46 and 50. The '817 patent is

directed to immunoregulation and reducing the rejection of tissue transplants, which is an entirely different mechanism from temporary p53 inhibition.

Because the '817 patent is directed solely to an immunoregulation action (column 3, lines 29-32), not temporary p53 suppression, and because these functions are so different, a person skilled in the art would have had no motivation to utilize a compound in the '817 patent disclosed as a reversible p53 inhibitor with any reasonable expectation of achieving successful therapeutic results as disclosed in the present application. Accordingly, the rejection of the claims as being unpatentable on the '817 patent should be withdrawn.

Claims 33 and 34 stand rejected as being anticipated under 35 U.S.C. §102(b) by a Chernov et al. publication (Chernov publication). The basis of this rejection is that because the Chernov publication teaches prevention of apoptosis by treating a host with a salicylate, this result is attributed (incorrectly) to reversible inhibition of p53. It is submitted that the rejection is in error, and that new claim 50 (which replaces claims 33 and 34) is neither anticipated by nor obvious over the Chernov publication.

As clearly stated in the abstract of the Chernov publication, salicylate "inhibits the activation of protein kinases and transcription factors involved in stress processes" and thereby inhibits both p53-dependent transcription and apoptosis. The Chernov publication goes on to states that "[T]he inhibition of transcription is due mainly to impairment of the ability of p53 to bind to DNA. The treated cells resume

their p53-dependent programs whenever the salicylate is removed, even after as long as 60 hours after DNA has been damaged. Also, see the Chernov publication, p. 2504, left-hand column, second full paragraph.

Importantly, the administered salicylate was *incapable* of preventing cell death, because apoptosis leading to cell death resumed immediately after salicylate removal (see Chernov publication, page 2505, right-hand column). Hence, salicylate does not provide any protection or survival benefit for cells, and, therefore, cannot be used or suggested for cell or tissue protection, as presently claimed.

The Chernov publication, therefore, not only fails to teach or suggest a compound that protects cells from stress-inducing events, the publication also absolutely fails to teach or suggest the use of a temporary p53 inhibitor to reversibly inhibit p53 activity, and thereby protect a cell or tissue from death by a stress-inducing event. In particular, the Chernov publication teaches that salicylate is not a specific (let alone a reversible) p53 inhibitor, but rather is a broad inhibitor of protein kinases and transcription factors involved in stress response, including, for example, NF-kappaB. Hence, even though the Chernov publication fails to teach protection of cells by administration of salicylate, if such cell protection was demonstrated, the protective effect could not be attributed to a p53 inhibitory activity, let alone a temporary p53 inhibitory activity.

Accordingly, because salicylate acts via a mechanisms different from temporary inhibition of p53 activity, and because salicylate fails to protect cells

from death attributable to a stress-inducing event, it is submitted that claims 46 and 48-50 are neither anticipated by nor obvious over the Chernov et al. publication, and that this rejection should be withdrawn.

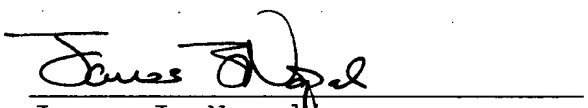
Applicants will provide formal drawings after receiving an indication of allowed claims.

It is further submitted that the claims are in proper form and scope for allowance. Early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP

By 

James J. Napoli
(Registration No. 32,361)
Attorneys for Applicants
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
(312) 474-6300

Chicago, Illinois
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